Remarks

Claims 1, 2, 6-16, 18 and 20-28 are pending. Claims 3-5, 7, and 19 have been canceled. New claim 29 has been added. Support for this new claim is found on page 5, line 28 to page 6, line 11 and page 18, lines 26-30. Claims 12-14 have been amended to depend from new claim 29. Claims 1 and 15 have been amended to remove the element "modified" and define the intein sequence as being fused to the carboxy-terminus portion of the extein. Support for this amendment is found on page 7, lines 12-28.

Rejection Under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1, 2, 6-16, 18 and 20-28 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicant respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003; *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.,* 857

F.2d 778 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.,* 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation ' must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

Claims 1, 2, 6-16, 18 and 20-28 satisfy the enablement requirement

Claim 1 is directed to a DNA construct for expressing multiple gene products that includes a promoter, multiple genes to be expressed (exteins), intein sequences to catalyze excision of the exteins and a transcription termination sequence. The specification teaches how to make this DNA construct on pages 18 and 19. The specification also teaches intein sequences that prevent ligation of the cleaved exteins (page 7, line 29 to page 8, line 19) as well as the reasons for modifying the intein sequences.

The enclosed declaration by Dr. Kristi D. Snell demonstrates that making and using the claimed DNA construct is enabled using the methods described in the specification. Specifically, Dr. Snell declares that one can make a DNA construct for expression of multiple gene products in a cell that includes a) a single promoter (*trc* promoter), b) multiple exteins (GFP and GUS), c) intein sequences (engineered for Ala cleavage) that prevent ligation of cleaved exteins, and a transcription termination sequence. This construct can catalyze excision of the exteins in a cell and the exteins are not ligated. This is demonstrated by western blot probed with antibodies to GFP and GUS. Western blot is the most appropriate assay to demonstrate intein-mediated cleavage because the molecular weights of the cleavage products can be resolved on an acrylamide gel.

The claims define an intein that can catalyze excision of exteins. This is a common feature of all inteins regardless of the mechanism of action. Southworth describes and alternative splicing mechanism for inteins but the function is still the same. The intein sequence can still "catalyze excision of exteins". The data in the Declaration by Dr. Snell demonstrates

that one can achieve excision of the exteins using the methods in the specification for creating the DNA construct. This feat is accomplished without undue experimentation and with a reasonable expectation of success. The courts have indicated that some experimentation is permitted as long as such experimentation is not undue. As stated in *MIT v. A.B. Fortia*, "The fact that experimentation may be complex does not make it undue if the art typically engages in such experimentation".

A proper analysis of the factors described in *In re Wands* shows that these claims satisfy the enablement requirement. The quantity of experimentation necessary to make and use the claimed DNA construct is not undue. All of the methods described are well known and routine to one of ordinary skill in genetic engineering. Experimentation is clearly necessary in the field of genetic engineering but it is critical to note that one of ordinary skill in this field is able to undertake a task such as ligating sequences in a DNA construct and expressing the construct in a host cell without *undue* experimentation. There is sufficient direction and guidance given by the specification to make and express the claimed DNA construct. The process of making the DNA construct and which sequences to use is described on pages 4-12 of the specification and in Example 1. The experimental protocols are routine in the art. Expression vectors are commerically available, restriction enzymes and ligation enzymes are commerically available. Intein sequences are known. Methods to modify nucleotide sequences are known. The level of skill of one in the art is high. One of skill in the art of genetic engineering would be very familiar with methods and protocols to create a DNA construct of several sequences and ligate

them together in the proper reading frame for expression in a vector. Gene expression is quite predictable in the art. Creating constructs and achieving expression in a host cell is commonplace. Recombinant DNA technologies would not enjoy the popularity they do if expression was not predictable.

Rejection Under 35 U.S.C. § 112, first paragraph (written description)

Claims 1, 2, 6-16, 18 and 20-28 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicant respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Legal Standard

"There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed". *Wertheim*, 541 F.2d at 262, 191 USPQ at 96 (CCPA 1976). The written description requirement for a claimed genus may be satisfied through a sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or a disclosed correlation between function and structure, or by a combination of such identifying

characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be a situation where one species adequately supports a genus. See, e.g., *Rasmussen*, 650 F.2d at 1214, 211 USPQ at 326-27.

The Federal Circuit has overturned the application of the written description requirement in the field of biotechnology originally set out in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In the patent context, not all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure. (*Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 Fed.Cir. 2003).

Claims 1, 2, 6-16, 18 and 20-28 satisfy the written description requirement

The claims are directed to using "modified intein sequences". The specification clearly describes on page 7-9 how to use available inteins (see page 8) for use in the claimed method. The method for making and using the claimed DNA construct is explicity described in Example 1 on page 18 of the specification. The genus of inteins is sufficiently described by the specification. The database of known inteins is described. Inteins that prevent ligation of

cleaved exteins ar also described. For example the intein from Mycobacterium xenopi GyrA and inteins modified by mutating serine 538 to alanine or glycine are described on page 8, lines 1-9. It has been stated in *Rasmussen* and recently affirmed in *Amgen* that it is not necessary to disclose the sequences of all claimed inteins in a genus.

The inteins are described on page 7-9 of the specification. The sequences of the inteins are known in the art and are easily accessible to one of normal skill, for example on GenBank. The mechanisms of intein-mediated cleavage and the sequences responsible for cleavage are also known in the art. One of skill in the art would read the specification and clearly determine that the Applicant were in possession of the claimed method and DNA construct at the time of filing.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1, 2, 6-11, 15-16, 18 and 20-28 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicant respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 1 and 15 have been rejected because the Examiner asserts that the metes and bounds of the term "modified" and "modified by fusing" are indefinite. Claims 1 and 15 have been amended to remove the term modified and define the intein as being fused to the carboxy-terminus portion of each gene except the last gene to be expressed.

Claims 1 and 15 have been rejected as being indefinite because the Examiner is unclear if an order of the genes is important to proper functioning of the DNA construct. The claims define

"Multiple genes, or exteins" that are followed by an intein sequence except for the last gene to be expressed. No order of the genes is important for proper function of the DNA construct. The only important feature is the presence of an intein between genes to be expressed. This is defined in the claims.

Rejection Under 35 U.S.C. § 102

Claims 1 and 15 were rejected under 35 U.S.C. § 102(b) as being anticipated by *J. Biol. Chem.* 1996 271:22159-22168, Chong *et al.* ("Chong"). Applicant respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Chong

Chong discloses a construct designed to express proteins in *E. coli* where the construct includes a first gene (maltose binding protein; MBP) fused to an intein and a second gene (thioredoxin) fused to an intein all of which are operably linked to a promoter sequence operable in *E. coli* and a transcription terminator. Chong fails to disclose any construct or method that uses intein sequences that catalyze excision of exteins and where no ligation of the products occurs. Chong attempts to arrest the splicing of the construct at specific stages, (see Figure 2) but Chong clearly fails to identify any proteins related to MBP and *E. coli* thioredoxin as separate entities.

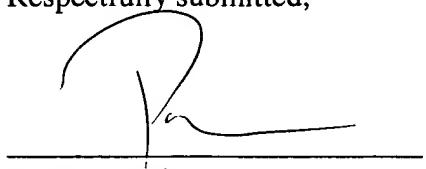
Claim 1 is directed to "a DNA construct for expression of multiple gene products in a cell... *wherein the exteins are not ligated*". The Examiner asserts that Figure 5 of Chong

discloses this feature. Lane 4 of the western blot in Figure 5 of Chong shows the different intermediates of the *in vitro* splicing reaction in the presence of dithiothreitol. This reaction has a 42 kDa band of the MBP gene product but also has a 56 kDa band of ligated MBP-thioredoxin products. Thus Chong does not disclose the claim element that the "exteins are not ligated". In this *in vitro* splice reaction, the exteins **were** ligated. Chong does not disclose all elements of the claimed DNA construct or its method of use and does not anticipate claims 1 and 15.

Furthermore, claim 15 is directed to a method for the expression of multiple gene products *in a cell*. The Examiner draws attention to Figure 5 to demonstrate the intein-mediated cleavage of one extein from the pre-protein. This cleavage reaction is performed *in vitro* (i.e. not in cell) and only in the presence of dithiothreitol (page 22165, column 1). Claim 15 is directed to cleavage in a cell. Dithiothreitol is cytotoxic and could not be used in a cellular expression system. Again, Chong does not anticipate claim 15.

- Allowance of claims 1, 2, 6-11, 15-16, 18 and 20-28 is respectfully solicited.

Respectfully submitted,



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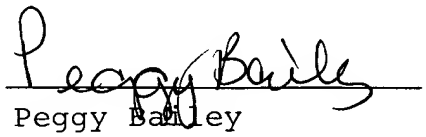
CERTIFICATE OF MAILING UNDER 37 CFR §1.10

I hereby certify that this Request for Continued Examination (RCE), and any documents referred to as attached therein, are being deposited with the United States Postal Service on this date, January 6, 2004 in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR 1.10, Mailing Label Number EL717745435US, addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.



Peggy Bailey

Date: January 6, 2004